REMARKS

Claim 1 has been amended to more particularly point out the amounts of the pharmaceutically active ingredient, the directly compressible dextrose monohydrate, and sucralose. Claim 1 was also amended to indicate that the active ingredient is contained in a matrix and that the matrix consists essentially of the compressible dextrose monohydrate and sucralose. Support for these amendments can be found throughout the specification at, for example, p. 3, lns. 10-12, p.3, ln. 29 – p. 4, ln. 6, and p. 5, lns., 4-6 and in the Examples.

Claim 12 has been amended to indicate that the active ingredient is contained in a matrix, to more particularly point out the amounts of the claimed components, and to set forth Markush group language for the claimed lists. Support for these amendments can be found throughout the specification at, for example, p. 3, lns. 10-12, p.3, ln. 29 – p. 4, ln. 6, and p. 5, lns., 4-6, and in the Examples.

No new matter has been added by the above amendment.

Obviousness Rejection

Claims 1-5 and 8-13were rejected under 35 USC §103(a) as being unpatentable over U.S. Pat. No. 6,270,790 ("Robinson") in view of U.S. Pat. No. 4,684,534 ("Valentine"). (Paper No. 20061005 at 3.)

For the reasons set forth below the rejection, respectfully is traversed.

Robinson has an effective filing date of August 18, 1998. McNeil-PPC, Inc. is the assignee of McNeil-PPC, Inc.

The captioned application was filed on December 29, 2000. McNeil-PPC, Inc. is the assignee of the captioned application.

It is submitted that Robinson and the captioned application were, at the time the instant invention was made, owned by or subject to an obligation of assignment to the same person. 1241 OG 96 (Dec. 26, 2000). Because the captioned application was filed on or after November 29,1999, the captioned application qualifies for the benefit of the §103(c)/102(e) exclusion of common assignee-type prior art. 1233 OG 54 (Apr. 11, 2000). Therefore, Robinson is un available as reference to reject the captioned application for obviousness. For this reason, the rejection is improper and should be withdrawn.

Claims 1, 3-5 and 8-13 were rejected under 35 USC §103(a) as being unpatentable over U.S. Pat. No. 6,667,050 ("Boissonneault") in view of Valentine. (Paper No. 20061005 at 5.)

For the reasons set forth below the rejection, respectfully is traversed.

Boissonneault discloses

(57) **ABSTRACT**

The present invention relates to a chewable, palatable oral contraceptive tablet, comprising an oral contraceptive agent, a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, as well as use of these tablets in a method of human female oral contraception, and in a method of enhancing compliance with a human female oral contraceptive regimen.

The oral contraceptive agent may be present in a carrier either in a dissolved or a uniformly suspended state. A carrier comprises all but the active oral contraceptive agent or agents and includes an inactive ingredient or a combination of one or more inactive ingredients. The carrier imparts chewable and palatable characteristics to the tablet and must be suitable for human consumption, that is, free of harmful amounts of any toxins or components that are adverse to humans. All ingredients in the carrier should be generally recognized as safe (GRAS), as determined by the Food and Drug Administration (FDA) or the Flavor and Extract Manufacturers' Association (FEMA). The carrier selected for the invention must be chewable and should not confer a disagreeable taste to the tablet. Thus, the carrier itself must be palatable. The primary ingredient of a carrier is one or more diluents. Non-limiting examples of diluents that can be used in accordance with this invention include microcrystalline cellulose, corn starch, modified starch, calcium carbonate, dicalcium phosphate, and poly-alcohol sugars such as dextrose, mannitol, sorbitol, xylitol, lactose, sucrose, and fructose. Many other diluents or other ingredients suitable as components of carriers for a chewable, palatable oral contraceptive tablet are available and would be well known to those skilled in the art in view of the present disclosure.

In another aspect of the invention, the tablet optionally further comprises at least one of a flavor agent, a sweetener, and a color agent. A flavor agent can be used to enhance the

A sweetener can also be used to enhance to taste of the tablet, making the tablet more palatable than a tablet without a sweetener. Sweeteners include natural sugars and artificial sugar substitutes. Non-limiting examples of sweeteners that can be used in accordance with this invention include aspartame, sucralose, xylitol, sorbitol, mannitol, dextrose, sucrose, and fructose. Non-limiting examples of the amount of flavor agents or sweeteners that can be used in the tablet composition of the present invention are listed in Table 2. The amounts in Table 2 are given as percentage of the total tablet weight.

TABLE 2

Sweetener and Flavor Amounts Used in Chewable Oral Contraceptive Formulations

Ingredient Type	Examples	Broad	Intermediate	Preferred
Sweetener	Aspartame	0.02 to 1.0%	0.02% to 0.2%	0.03% to 0.05%
	Sucralose	0.01 to 0.5%	0.01% to 0.1%	0.02 to 0.04%

contraceptive agent ingredient(s).

Binders aid the formation of granulated particles of active oral contraceptive agents and carrier ingredients. Non-limiting examples of binders include glucose, acacia, guar gum, gelatin, simple syrup, sucrose, sorbitol, starch, alginic acid, alginate salts, polyethylene glycol, polyvinylpyrrolidone, polymethacrylates, pregelatinized starch, and celluloses such as methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and ethylcellulose. A solution of binder is prepared (concentrations dependent on the particular binder used), and the binder solution is mixed with the other excipients to form the wet granulation. A binder such

Col 6.

Disintegrants facilitate breakup of the tablet after administration during chewing. Non-limiting examples of disintegrants include crospovidone, croscarmellose sodium, starches, corn starch, potato starch, modified corn starch, sodium starch glycolate, and pregelatinized starch. Disintegrants can be included in the tablet formulation in amounts generally less than about 25% of the tablet weight, preferably less than about 20%, and more preferably about 1 to about 20% (natural starches such as corn or potato starch), about 5 to about 10% (pregelatinized starch), and about 3 to 8% (modified corn starch). Crospovidone and croscarmellose sodium are used at levels of about 5% or lower.

As a final step in the manufacture of the tablet, a lubricant, an anti-adherent, and a glidant can be added to the tablet

Id.

A tablet made in accordance with the present invention may simply be chewed. This substantially reduces the existing barriers to compliance. The use of a chewable, palatable tablet in accordance with the present invention eliminates the need to incorporate liquid to facilitate swallowing and makes oral contraceptives more agreeable for patients who have difficulty or reluctance to swallowing tablets. The

Col. 9

Compositions that have been prepared in accordance with this invention are given in Examples 1–2. Additional examples of compositions that can be formulated in accordance with this invention are given in Examples 3–6.

Id.

One technique of making the tablets of the present invention is a wet granulation technique. In a wet granulation technique, the active oral contraceptive agents are blended in a solution of binder which is then blended with the diluent(s) to form a wet granulation. After drying, the granulation is blended with the flavor ingredient(s), the disintegrant, the lubricant and any other optional ingredients. The final blend is compressed into tablets. This wet granulation method is exemplified by Examples 1 and 2.

Alternatively, a dry granulation technique can be used. In a dry granulation technique, the active oral contraceptive agents are blended with the diluent(s) to form a dry granulation. This is then blended with the flavor ingredient(s), the lubricant and any other optional ingredients, and finally compressed into tablets. This dry granulation method is exemplified by Examples 3, 4 and 5.

Alternatively, the active pharmaceutical ingredients are wet granulated as described previously, then blended with additional diluent(s) to form a dry granulation. This is then blended with the flavor ingredients, the lubricant and any other optional ingredients, and finally compressed into tablets. This method is exemplified by Example 6.

Col. 10

EXAMPLE 4

Composition of a 100 milligram tablet

Ingredient Type	Ingredient	Amount (milligrams/tablet)
Oral Contraceptive Agent	Norethindrone	0.40
Oral Contraceptive Agent	Ethinyl Estradiol	0.035
Diluent	Mannitol	97
Flavor Agent	Strawberry	2
Lubricant	Magnesium stearate	0.5

EXAMPLE 6

Composition of a 100 milligram tablet

Ingredient Type	Ingredient	Amount (milligrams/tablet)
Oral Contraceptive Agent	Norethindrone	0.40
Oral Contraceptive Agent	Ethinyl Estradiol	0.035
Diluent	Dextrose	60
Diluent	Lactose	37
Flavor Agent	Strawberry	2
Lubricant	Magnesium stearate	0.5

Valentine discloses

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide a tablet which stores well and liquifies quickly when used, particularly a tablet which liquifies quickly in the mouth upon chewing and is pleasant tasting.

It is another object of the present invention to provide a tablet by direct compression which includes a substantial quantity of an active ingredient, particularly an active ingredient which in its raw material form is a powder that can not be compacted into a cohesive tablet easily or at all.

It is still another object of the present invention to provide agglomerates from which such tablets can be directly compressed and to provide processes for making such agglomerates.

forms.

The carbohydrate-based agglomerates comprise carbohydrate particles selected from the group consisting of dextrose, dextrose monohydrate, maltodextrine, fructose, sucrose, lactose, maltose and xylose; and a water-soluble binder selected from the group consisting of maltodextrine, corn syrup solids, dextrose, sucrose, polyvinylpyrollidone and cooked starch paste. The

Col. 2.

The term "active ingredient" is used herein in a broad sense and encompasses any material which can be carried by or entrained in the agglomerate. For example, an active ingredient can be a pharmaceutical such as an antacid, analgesic or drug; or a flavor, breath sweetner, vitamin, dietary supplement, or nutrient; or the like and combinations thereof. Active ingredients include but

Col. 3

saliva.

A process for making the carbohydrate-based agglomerate comprises the steps of forming a fluidized bed of the carbohydrate particles, intermittently spraying a solution of the water soluble binder in a droplet size of from about 20 microns to about 100 microns into the fluidized bed so as to cause intimate comingling of solution and carbohydrate particles and adhesion together of carbohydrate particles to form agglomerated particles, drying the particles in the fluidized bed between intermittent sprayings, and continuing spraying and drying until the desired amount of solution has been sprayed into the bed. Thereafter, the agglomerated particles are dried to a desired moisture content or the equilibrium moisture content. The amount of liquid binder solution sprayed corresponds to a binder content in the agglomerate of from about 1 percent to about 10

Id.

A process for making a tablet from the finished carbohydrate-based agglomerates described above including from about 0.4 percent to about 1.0 percent of a lubricant, comprises compressing the agglomerate particles with entrained active ingredient and lubricant in conventional tablet-forming apparatus to a hardness sufficient to hold the tablet together and substantially destroy the open pore structure of the agglomerate at the surface of the tablet while substantially maintaining the open pore, i.e., large surface area, structure of the agglomerate in the interior of the tablet. Thus, the agglomerate is compressed so that the interior of the tablet retains the essential porous structure and other physical characteristics of the agglomerate which enable it to liquify quickly, while the physical characteristics of the agglomerate are changed primarily at the surface of the tablet.

Col. 4.

In making the rejection, the Examiner asserted that Boissonneault "teach[es] a chewable tablet composition comprising an active ingredient and carriers such as dextrose." (Paper No. 20061005 at 5.) The Examiner further stated that Boissonneault's Examples contain sucralose and it "teaches the same binders and disintegrants that are also claimed in the instant invention." (*Id.*)

The Examiner admitted that Boissonneault did not disclose dextrose monohydrate. To fill the acknowledged gap, the Examiner looked t Valentine.

The Examiner asserted that Valentine "teaches a chewable tablet composition comprising excipient base materials such as carbohydrate based agglomerate materials including dextrose, dextrose monohydrate..., which are held together by small quantitites of binding materials." The Examiner further asserted that the carbohydrate agglomerates area in the size range of 20 to 100 microns.

The Examiner concluded that "it would have been obvious for one of [] ordinary skill in the art at the time [] the instant invention was made that the particulate

agglomerated carbohydrates such as dextrose or dextrose monohydrate are equally effective for compressibility" The Examiner reasoned that the skilled artisan would have employed particulate dextrose or dextrose monohydrate because Valentine suggests that the carbohydrates enable the tablets to be highly compressible and also the tablets readily dissolve in minimal amount of water." The Examiner further characterized the ration of amounts of dextrose monohydrate and sucralose as being mere optimization.

As is fundamental, a *prima facie* case of obviousness must be based on facts, "cold hard facts." When the rejection is not supported by facts, it cannot stand.

Initially, it is noted that the claims affirmatively require, among other things, **directly compressible** dextrose monohydrate (emphasis added). The rejection fails to identify where in Boissonneault or Valentine such a limitation can be found. At most, the rejection summarily concludes that "particulate **agglomerated** carbohydrates such as dextrose or dextrose monohydrate are equally effective for compressibility." (emphasis added). (*Paper No. 20061005 at 5-6*).

The mere fact that Valentine includes dextrose monohydrate in a list of possible carbohydrate particles that are used to make the carbohydrate-based agglomerates is not a disclosure or suggestion of a **directly compressible** dextrose monohydrate.

According to Valentine, after being formed, the carbohydrate-based agglomerates "have particular utility as a direct compression agglomerate from which tablets…can be made." (*See* Valentine, col. 3, lns. 48-51.) The fact that the dextrose monohydrate must be formed into an agglomerate before being compressed indicates that it is not **directly compressible**. Therefore, the rejection is improper and should be withdrawn.

Additionally, when a rejection depends on a combination of references, there must be some teaching, suggestion, or motivation to combine the references. Stated another way, the prior art as a whole must "suggest the desirability" of the combination. The source of the teaching, suggestion, or motivation may be "the nature of the problem," "the teachings of the pertinent references," or "the ordinary knowledge of those skilled in the art."

The rejection uses Valentine to fill in the acknowledged gaps left by Boissonneault. However, it is not seen where there is any expectation of success to use dextrose monohydrate from Valentine in Boissonneault's dry granulation Examples. As

disclosed in paragraph [0021] of the captioned application, dry granulation is a method to make tablets according to the claimed invention. One reason for this is that Valentine discloses the use of a fluidized bed to make the carbohydrate-based agglomerate. It is not believed that dry granulation and fluidized bed technology are similar. Nor is it believed that the use of a particular composition in one technology, e.g., fluidized bed, would provide any expectation of success in a different technology, e.g., dry granulation. This is particularly applicable as far as dextrose monohydrate is concerned and, even more particularly, directly compressible dextrose monohydrate is concerned. For these additional reasons, the rejection is improper and should be withdrawn.

Even if the Examiner made a *prima facie* case of obviousness, which is strongly denied for the reasons set forth above, the data provided in the captioned application overcomes such a rejection.

The Examiner attempted to equate dextrose and dextrose monohydrate for use in the present invention. Accepting this proposition as true for the sole purpose of this line of reasoning, it is noteworthy to review Tablet 1 and Tablet 2 in the Examples section of the captioned application. The only difference between Tablet 1 and Tablet 2 is that Tablet 1 uses dextrose monohydrate and Tablet 2 uses mannitol.

The data from people who evaluated the samples show that Tablet 1 was smoother, not as dry, not as gritty and preferred overall to Tablet 2. Thus, dextrose monohydrate performed better than mannitol.

Turning to Boissonneault, Examples 3, 4, and 5 were tablets made by dry granulation, a method that can be used to make tablets according to the claimed invention. Examples 3 and Example 5 (listed as the first instance of a duplication of the title "Example 6" in col. 11 at ln. 14.) each use dextrose and Example 4 uses mannitol. According to these Examples dextrose and mannitol would be considered equivalent in the formulations disclosed in those Examples.

Since it is accepted only for this line of reasoning that dextrose and dextrose monohydrate are "equally effective", based on Boissonneault's dry granulation Examples 3-5, dextrose monohydrate and mannitol would also be considered "equally effective." However, as seen from the data of the instant application, directly compressible dextrose monohydrate and mannitol are not "equally effective" in tablets made according the

claimed invention. Thus, given the surprising and unexpected results that the present invention produced, the claimed invention is patentable and the rejection should be withdrawn.

Finally, the Examiner is invited to call the applicants' undersigned representative if any further action will expedite the prosecution of the application or if the Examiner has any suggestions or questions concerning the application or the present Response. In fact, if the claims of the application are not believed to be in full condition for allowance, for any reason, the applicants respectfully request the constructive assistance and suggestions of the Examiner in drafting one or more acceptable claims pursuant to MPEP § 707.07(j) or in making constructive suggestions pursuant to MPEP § 706.03 so that the application can be placed in allowable condition as soon as possible and without the need for further proceedings.

Respectfully submitted,
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